Aus dem Forschungslaboratorium der Neurologischen Universitäts-klinik Basel
(Direktor: Prof. Dr. F. Georgi)

The Combined Hippuric Acid Test in Patients with Liver Disease, Neuritis and Discus Hernias

Inaugural Dissertation
zur Erlangung der Doktorwürde der Medizinischen Fakultät der
Universität Basel

vorgelegt von
Joel Karp
von New York (USA)

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Introduction

It has been shown that liver disease has been discovered in various mental as well as organic nervous diseases. By the use of various liver function tests, attempts have been made to determine the cause of these liver disturbances. One such test for liver function has been the combined Quick hippuric acid test in the modification of *Georgi* et al, (2) and *Rieder* (11).

Method

The principle behind the Quick hippuric acid test is as follows: The accumulated benzoic acid in a person is detoxified by its coupling onto glycine and the resulting hippuric acid being excreted. The coupling of benzoic acid and glycine to form hippuric acid is not specifically performed by the liver. The kidneys can perform the same function. But the process of making glycine available so that it can then be coupled onto benzoic acid is a function that the liver is alone responsible for. It is the specific function of the liver to mobilize the glycine for its ultimate coupling to the benzoic acid. In order to exclude other dysfunctions and to claim with certainty that there is a malfunction of the liver to mobilize glycine one must perform both the classical and the modified Quick tests. In the classical Quick test the patient receives only sodium benzoate and he mobilizes the necessary glycine to detoxify the sodium benzoate. In the modified Quick test the patient receives sodium benzoate plus one equivalent of glycine *(Georgi et al. 5)*. The patient therefore, does not have to mobilize any glycine himself, but has only the task of coupling both compounds. *Menkes* (7) points out that a glycine disponibility disturbance is definitely detected by employment of both the classical hippuric acid test and the modified hippuric acid test. Formally, in carrying out the modified hippuric acid test 6 g. of glycine were given to each patient. In the improved

modified hippuric acid test only 3 g. of glycine = equimolar amount, is given to each patient. The patient's body does not have to mobilize glycine, it merely has to couple both components. One can speak of a true glycine mobilization dysfunction, when the classical hippuric acid test reveals a pathological value and the modified hippuric acid test shows values which range within the norm. If normal values are received in the modified hippuric acid test it conjointly shows that factors such as malabsorption, frailty in enzymes in regard to the coupling reaction in the liver and kidney, defective excretion (kidney) are not causes for pathological values in the classical hippuric acid test. Pathological results in the modified test tend to point towards renal disease. What we have to consider when evaluating the results in the Quick test is the volume of urine excreted by the patient. *Rieder* (11) has clearly demonstrated in his survey of 267 peroral hippuric acid determinations on normal persons of both sexes that the urine volume must be considered in order to prevent errors and misinterpretation of the results. Rieder performed 172 classical Quick tests on 140 individuals, and 95 modified Quick tests on 81 individuals. From the range of Rieder's tests which varied between 200 to 1600 cm^3 of urine, a shifting of the volume of about 1000 cm^3 led to a shifting of the benzoic acid figure of approximately 0.7 g. Rieder also points out that after this correction the effects of age and body weight do not influence the results. *Rieder* (12) questions the reliability of the results of the Quick hippuric acid tests obtained via the intravenous route. He performed 59 double trials, one intravenous and one peroral application on the same person. The results showed twice as great a dispersion as the oral test. This investigation, therefore, refers only to the oral test results.

Brief Review of the Literature on the Quick Hippuric Acid Test

The value of liver function tests lies in their ability not only to inform one of hepatic disease, but to give the examiner an understanding of the exact physiology of certain liver functions. In this way he may be better equipped to make a differential diagnosis and also may be able to give some information as to the prognosis of the affliction.

Quick (9), reporting on 7 cases of catarrhal jaundice showed that the results of the test run parallel with the clinical course. Recovery occurred in from 4 to 6 weeks, and at this time the synthesis of hippuric acid is normal. Quick also examined 12 cases with malignant processes and 20 cases of cholecystopathy. Of the 12 cases with malignant processes, 11 presented a diminution of function according to the classical hippuric acid test. The explanation for the exception is that the disturbancy of function is due primarily not to a destruction of parenchymal tissue, but rather to the toxins arising from the malignant process.

Of the 20 cases of cholecystopathy examined by Quick, it was noted that the hippuric acid production was not impaired in cases of cholecystitis and obstructions of the common bile duct by stones caused no definite impairment of liver function.

Quick also performed the test on 42 patients who did not present hepatic damage in order to establish that diminished production of hippuric acid is due only to liver damage. In none of the patients examined was there a marked lowering of the production of hippuric acid. In 1932 Quick found that the excretion of hippuric acid proceeded at a constant rate irrespective of the amount of sodium benzoate administered. He found that the output of hippuric acid was greatly increased by the ingestion of glycine or foods rich in it. The conclusion was that the rate of formation of hippuric acid depended on the speed with which the organism can synthesize glycine. Since the main site of synthesis of glycine is the liver, Quick reasoned that various degrees of hepatic damage would show a corresponding diminution in the excretion of hippuric acid.

Boyce and McFetridge (1) report that in the presence of renal disease, the test should be checked from that standpoint. Quick suggests to determine the non protein nitrogen. *Kohlstaedt and Helmer* (6) prefer the urea clearance, because as much as 20% renal damage can occur without alteration of the non protein nitrogen content of the blood. If renal damage is present, the hippuric acid is retained as a nitrogenous product and the test must be interpreted in the light of that fact. *Sherlock* (15) also points out that both kidneys and liver take part in hippuric acid metabolism, and even if hippuric acid is not synthesized by the kidneys, its ultimate excretion demands adequate renal function. In Basle, the combined hippuric acid test in the modification of *Georgi et al* (5) is performed in order to eliminate the kidneys as a site of hippuric acid production.

Scurry and Field (14) point out that the excretion of hippuric acid normally varies with the size of the individual. The correlation between age and the quantity of hippuric acid being excreted was already reported upon. Their results on 6 patients of 56 years or over who had no apparent evidence of liver or kidney disease, reveal that these patients excreted an average of 70.3% of the amount of hippuric acid predicted from their surface area. This apparently suggests that in older people there is physiologically some atrophy of the liver which causes some impairment in the response to the hippuric acid test of liver function. Their results, however, suffer from the fact, that they used non volume corrected values for their interpretation. *Rieder* (11) tested the effect of age (between 17 and 66 years) and body weight (between 48 and 90 kg) on the volume corrected results of the classical and modified Quick tests and found that neither factor influences the results.

The liver plays a very important role in all types of surgical disease. *Boyce and McFetridge* (1) therefore believe that one should consider the liver in evaluating the surgical risk as it is to consider the heart, kidneys and lungs. It is also known that the effect of anaesthesia may cause liver damage. Boyce and McFetridge report on normal persons undergoing elective operations (appendectomy or hernioplasty) not connected with the biliary tract. These patients received neither pre-operative nor special post operative treatment. The hippuric acid test was performed on these patients and the results showed a 25% drop in hepatic function. This could be attributed to the anaesthesia because hyperglycemia occurs after ether anaesthesia and is the result of loss of glycogen from the liver. Ether decreases the secretion of bile and suppresses other liver functions, namely urea formation. This impairment of liver function may be prevented by administering carbohydrates, particularly dextrose before and immediately after operation. According to the observations of Boyce and McFetridge in 6 cases with carcinoma of the head of the pancreas the hepatic function was reduced in some instances to 20% or less of normal values. Upon feeding dextrose orally and intravenously there was an increase of hepatic function.

In order to correctly interpret and treat various complications following operative procedures in the biliary tract an understanding of the physiological activities of the liver is required. *Vaccaro* (17) reporting on 4 cases following operation for common bile duct obstruction, found that post operative nausea failed to disappear. The patients became toxic, drowsy and one even became semistuporous. The patients were finally relieved by administration of glucose intravenously. The causes of their symptoms were believed to be noxious substances which were absorbed from the gastro-intestinal tract with a concomitant impairment of the detoxifying function of the liver. Vaccaro used the Quick hippuric acid test as a method for the detection of hepatic damage. Forty-four cases were examined by Vaccaro. Ten cases were clinically free of hepatic and renal disease and these were used as control cases to establish the normal output of hippuric acid. Twenty-seven cases revealed inflammatory disease of the gall bladder. Three cases revealed carcinoma. One case revealed chronic passive congestion of the liver. Vaccaro found that the results of the Quick test rather consistently bears out the condition of the liver. The excretion of hippuric acid was found by Vaccaro to be within normal limits in biliary tract disease where the liver appeared normal. A definite inhibition was noted in practically all cases presenting gross structural changes of the liver. The degree of inhibition corresponded to the amount of hepatic damage. In cases of biliary obstruction, all showed a lowered output. A diminished excretion resulted in carcinoma, cirrhosis and chronic passive congestion of the liver.

Snell and Plunkett (16) studied various patients with hepatic disease as to the excretion of hippuric acid. The correlation of the hippuric acid test and the reversal of the albumin/globulin ratio is of interest, since it is believed that this phenomenon is often associated with advanced hepatic damage. The patient with the smallest elimination of hippuric acid had a reversal of the albumin/globulin ratio and a reduction of the amount of total protein in the blood serum. Twenty cases of surgical types of jaundice were studied by Snell and Plunkett via the Quick test. The test can be useful to indicate the degree of hepatic damage and would be of considerable clinical value in determining surgical risk. In the cases with obstructive jaundice caused either by stone, stricture or carcinoma or in the cases of cholecystitis and cholelithiasis the Quick test revealed below normal value excretion of hippuric acid. These results are in agreement with those found by *Vaccaro* (17) in practically all cases presenting structural changes of the liver. These results would indicate that the Quick test is an accurate and satisfactory test for determining parenchymal hepatic destruction.

Kohlstaedt and Hellmer (6) report on 22 cases of diseases of the biliary tract, all of which were operated upon. In the cases of normal liver function the post operative reaction was mild and recovery was uneventful. In 2 cases of low liver function, death occurred. In 3 cases of cholelithiasis and cholecystitis, tests were made after the patients had completely recovered from surgery. In none of these had hepatic function which had been lowered preoperatively, returned to normal. One can therefore draw the conclusion that in cases of cholelithiasis and cholecystitis surgery offers a greater risk when there is evidence of an impaired detoxicating mechanism as shown in the hippuric acid test.

Georgi et al (2), (3), has shown that hepatopathies have been found in a number of mental nervous diseases. *Georgi* (2) performed the classical Quick test 99 times on 73 cases of schizophrenia and in the same number of cases he performed the modified Quick test 84 times. The results showed that most schizophrenics displayed a weakened capacity of making glycine available to be coupled onto benzoic acid. *Müller* (8) confirms the results of Georgi in his study of 158 acute and chronic schizophrenics by means of the Quick hippuric acid test based on volume corrected values according to Rieder. His results suggest a disturbance of mobilization of glycine, particularly in the acute exacerbations.

The review of the past literature has shown that the classical and modified Quick tests are of immense value in giving us information regarding the physiology of the liver. The combined hippuric acid tests are of value in determining liver function in organic as well as in neurological or psychiatric diseases. The combined tests can be used as a liver function test in combination with the other available methods to study the mechanisms of the liver.

Results

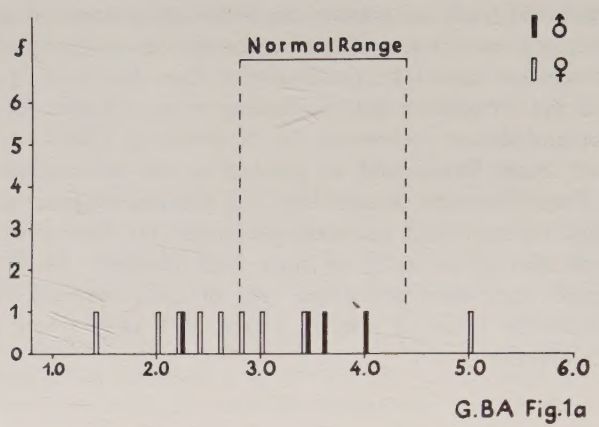
This statistical work summarizes the behavioral pattern of patients with liver disease, polyneuritis and discus hernias in the combined hippuric acid test. The case histories of 13 patients with liver disease, 13 patients with polyneuritis and 24 patients with discopathy were reviewed. These patients were either ambulatory patients at the Neurological Clinic of the Faculty of Medicine, Basle, Switzerland, or patients at the neurological division at the Felix Platter Hospital, Basle. Both the classical hippuric acid test and the modified hippuric acid test were performed on these patients and the results were used as an index of their liver function. In 7 cases, other liver function tests were performed. All of these revealed values which ranged within the limits of normal, except in 2 cases where pathological values were obtained.

Hepatopathy

We have divided the patients according to their sex and according to the performed procedure, whether it be the classical hippuric acid test or the modified hippuric acid test. Of the 9 female patients examined via the classical hippuric acid test, 5 patients revealed pathological values, whereas 1 male of the 4 males examined showed a pathological value. (Fig. 1a).

Upon examining the results of the modified hippuric acid test, we find that all cases of males and females examined, revealed values which ranged within the normal spectrum. (Fig. 1b).

It is interesting to note that in the classical hippuric acid test, the percentage of females with pathological values outnumber those of their male counterparts. The explanation for such results could possibly lie in the past medical histories of the patients. As *Vaccaro* (17) points out in his observations in cases of biliary obstruction a lowered output of hippuric acid is noted. It is known that females are especially prone to cholecystopathy, and via biliary obstruction liver damage could have been produced. The fact that liver damage was present in these patients is borne out when the results of the modified hippuric acid test are examined. By performing the modified hippuric acid test we eliminate the function of the liver to produce glycine, a function which for the liver alone is responsible, *Rieder* (10, 11, 12). One may therefore draw the conclusion that the female patients seem to show a typical liver dysfunction to mobilize glycine for the detoxification of benzoic acid.



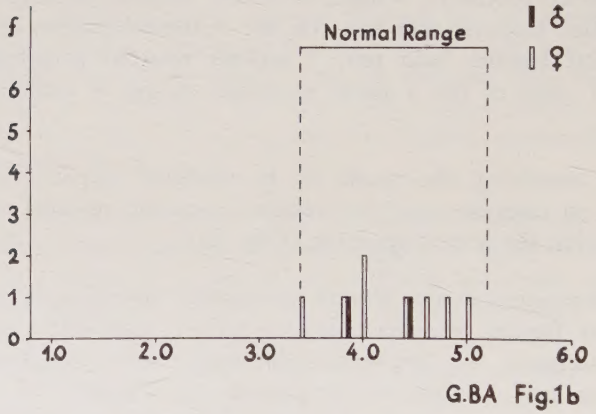


Fig. 1a Distribution of values in the classical hippuric acid test performed on 13 patients with hepatopathy.

Fig. 1b Distribution of values in the modified hippuric acid test performed on 10 patients with hepatopathy.

Ba: g. Benzoic Acid

F: Number of persons

Polyneuritis

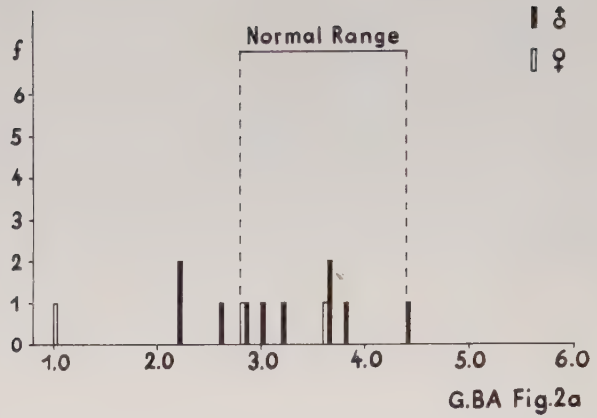
Ten males and 3 females were examined via the classical hippuric acid test. 3 male patients revealed pathological values. One female revealed a pathological value. (Fig. 2a).

Upon performing the modified hippuric acid test, we find that 3 of 7 males examined, likewise showed pathological values. Only 2 females were examined via the modified hippuric acid test and both revealed normal values. (Fig. 2b). From the above we may conclude that the 3 males who were unable to reach normal values under the addition of exogenous glycine, seemed to be suffering from renal disease rather than liver disease.

Discus Hernia

The results produced by the classical hippuric acid test on 14 males suffering from discus hernia reveal that 5 males produced pathological values. Of the 10 females examined via the same procedure, only 1 female produced a pathological result. (Fig. 3a).

In the modified hippuric acid test 9 males were examined and 3 of them showed below normal values. One male patient produced a hippuric acid value which lay beyond the normal boundaries. Only 2 females of 9 examined, produced below normal hippuric acid values. (Fig. 3b).



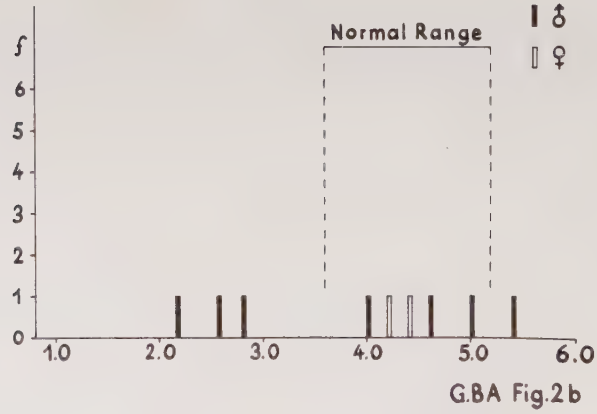
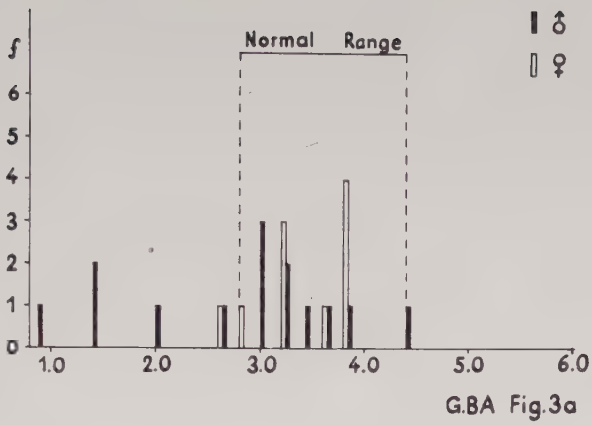


Fig. 2a Distribution of values in the classical hippuric acid test performed on 13 patients with polyneuritis.

Fig. 2b Distribution of values in the modified hippuric acid test performed on 9 patients with polyneuritis.

Ba: g. Benzoic Acid

F: Number of persons



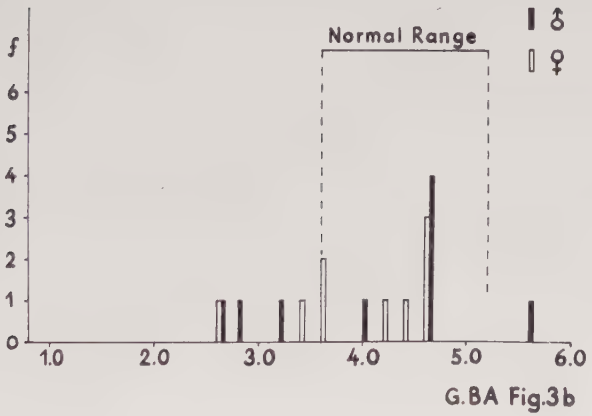


Fig. 3a Distribution of values in the classical hippuric acid test performed on 24 patients with discus hernia.

Fig. 3b Distribution of values in the modified hippuric acid test performed on 18 patients with discus hernia.

Ba: g. Benzoic Acid

F: Number of persons

Discussion

As can be seen by the literature the classical hippuric acid test will reveal pathological values, if definite parenchymal liver damage has taken place. Our results of patients afflicted with neurological disorders demonstrate that in those, where there is no evidence of corresponding liver damage, hepatic tests may also reveal pathological values. The combined hippuric acid test is one examination that strives to detect such liver disturbances.

Upon examining the results of the modified hippuric acid test, we find that the patients with hepatic disease, polyneuritis, as well as those with discus hernia, tend to fall back within the normal range. All of the patients examined with hepatopathy returned to values which ranged within the norm. This indicates that these patients reveal true glycine mobilization dysfunction. On the contrary we find 3 males among the patients with polyneuritis and 3 males and 2 females among those with discus hernia with pathological values. By performing the modified hippuric acid test, the body does not have to mobilize glycine, and all patients should show normal results of hippuric acid excretion. The above results suggest that among those patients who revealed pathological values on the modified hippuric acid test other mechanisms are not functioning properly, other than the failure of one's own body to mobilize glycine to be coupled onto benzoic acid. Among the mechanisms that may not be functioning properly, are the actual coupling mechanism of glycine onto benzoic acid, failure in proper resorption, failure of the kidney to concentrate by the elimination of hippuric acid. We have received an unexpected high number of pathological values in the modified hippuric acid test among the patients suffering from polyneuritis and discus hernia. These results reveal that the body is damaged to a far greater extent than is generally accepted. The results show that in approximately one-half of the cases with pathological values in the modified hippuric acid test the disturbance does not lay in the liver function, but is mainly that of renal interference. *Menkes* (7) observed in his examinations of patients suffering from alcoholism that organic malfunction was present in $\frac{1}{3}$ of his cases, and a genuine glycine disponibility dysfunction in only 10% of the cases.

Although in the above discussed problem the results cover a modest number of cases, there were in total 118 hippuric acid tests on 3 groups of ailments performed. The fact that the results seem in cohesion with the hitherto ascertained values by other neurological afflictions, especially the large series of examinations with the combined hippuric acid test on patients afflicted with multiple sclerosis and schizophrenia is not uninteresting. It emerged from the examinations of *Georgi and Beuthien* (4), *Müller* (8), *Rieder* (10) that an average of 40-70% of the patients revealed pathological hippuric acid values, depending upon the severity of the con-

dition and the length of the illness. In our results we find that the severity of the case and the duration of the malady did not have any influence upon the results of the combined hippuric acid tests. In the majority of the above mentioned cases with multiple sclerosis and schizophrenia, we are predominantly dealing with patients who reveal true glycine mobilization dysfunction, by which the classical hippuric acid test alone displays pathological values. As was expected out of our own cases of patients suffering from hepatic disease, the results emerged that half (6 out of 13) the patients show genuine glycine mobilization dysfunctions, while the kidney function remained intact. The other 27 patients behaved in a completely opposite direction. Four of these 27 patients revealed a true glycine disponibility dysfunction, while 8 via the combined hippuric acid test revealed kidney malfunction. If we examine these 27 patients with regard to their individual ailments, we can establish that of 13 patients, suffering from polyneuritis, renal malfunction is discovered in 3 of these patients, while only a single patient showed a glycine disponibility dysfunction. We certainly do not go wrong to trace back such a small percentage of liver or kidney dysfunctions to the numerous intoxications of a general nature. Moreover we have to cling to the fact that among such intoxications, a liver dysfunction was revealed only once among 13 patients; this result certainly should be verified on a sufficiently larger number of cases. Our analysis unexpectedly revealed the result that among 24 patients with discus hernia, similarly only in ¼ of the cases pathological values were revealed and among them only 3 patients showed genuine glycine disponibility dysfunction. Further clarification of these cases showed that 2 of these patients revealed high serum bilirubin values plus positive takata reactions; however the blood pressure in all cases showed a normal dispersion. In these 5 cases, there is no available evidence in the case histories to explain the results of a positive hippuric acid test.

If we can once again recollect the number in the above mentioned cases of multiple sclerosis and schizophrenia we find that the examinations reveal the following results: The combined hippuric acid test proves to be a rather sensitive reagent for the establishment of glycine disponibility dysfunction. This statement is supported by our findings that in neurological afflictions of a periphoral or local nature, such as polyneuritis and discus hernia, a pathological result relative to liver dysfunction is only exceptionally found. On the other hand, the negative results obtained in about 90% of our cases give indirect evidence that due importance should be given to the combined hippuric acid test, as can be seen in patients with unknown toxic disturbances present in usually more than 50% of the cases of multiple sclerosis and schizophrenia.

I would like to express my gratitude to Dr. H. P. Rieder for his inspiration and guidance of this work. I also would like to thank Prof. F. Georgi, chief of the Neurological Clinic, Basle, for his personal interest

and encouragement in carrying out this paper as well as for his valuable criticism.

Summary

1. Patients suffering from liver disease, polyneuritis and discus hernia were examined by means of the combined hippuric acid test as modified by Georgi and Rieder. 118 hippuric acid tests have been performed on 50 patients.

2. In the evaluation of the results, the patients were divided according to their sex.
Pathological values were obtained:

   a) in 5 female patients of 9 examined and 1 male of 4 examined with liver disease.

   b) in 3 males of 10 examined and 1 female of 3 examined with polyneuritis.

   c) in 5 males of 14 examined and 1 female of 10 examined.

3. All patients with hepatopathies revealed genuine glycine mobilization dysfunction, which is confirmed by the fact that upon performing the modified hippuric acid test (with the addition of glycine) all values are normalized.

4. An unexpected high number of pathological values were obtained among patients suffering from polyneuritis and discus hernia in the modified hippuric acid test, which tends to point out disturbances of renal function rather than liver dysfunction.

5. We come to the conclusion that the combined hippuric acid test is a sensitive reagent to detect glycine disponibility dysfunction, a liver disturbance, which often is not detectable by other conventional liver function tests.

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